Cochrane Library

Cochrane Database of Systematic Reviews

Prophylactic paracetamol for the prevention of fever in children receiving vaccination as part of a standard childhood immunization schedule (Protocol)

Kirubakaran R, Viswanathan A, Kompithra RZ

Kirubakaran R, Viswanathan A, Kompithra RZ.

Prophylactic paracetamol for the prevention of fever in children receiving vaccination as part of a standard childhood immunization schedule.

Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD012655.

DOI: 10.1002/14651858.CD012655.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Prophylactic paracetamol for the prevention of fever in children receiving vaccination as part of a standard childhood immunization schedule

Richard Kirubakaran[1], Anand Viswanathan[1], Rajeev Z Kompithra[2]

[1]Cochrane South Asia, Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India. [2]Department of Child Health, Christian Medical College, Vellore, India

Contact address: Richard Kirubakaran, Cochrane South Asia, Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Christian Medical College, Carman Block II Floor, CMC Campus, Bagayam, Vellore, Tamil Nadu, 632002, India. richrichigo@gmail.com.

Editorial group: Cochrane Upper GI and Pancreatic Diseases Group.
Publication status and date: New, published in Issue 5, 2017.

Citation: Kirubakaran R, Viswanathan A, Kompithra RZ. Prophylactic paracetamol for the prevention of fever in children receiving vaccination as part of a standard childhood immunization schedule. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No.: CD012655. DOI: 10.1002/14651858.CD012655.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To evaluate the efficacy and safety of prophylactic paracetamol to prevent fever in children receiving vaccination as part of a childhood immunization schedule.

BACKGROUND

Description of the condition

Children are given vaccines to prevent specific infectious diseases during their childhood. Despite benefits of long term protection, children are at risk of developing fever and other adverse events following any vaccination (Kelso 2012). Vaccination schedules vary across countries and regions. The World Health Organization (WHO) recommends at least 10 vaccines for routine immunization for children (WHO 2016). Of these, some antigens are administered as simultaneous multiple vaccines and as combination vaccines (Wallace 2014). Certain types of vaccines, such as the whole-cell pertussis vaccine have a higher risk of causing fever (Zhang 2014), up to 24.3% as compared to 7.3% with acellular vaccines (WHO 2015). Although most post-immunization fevers are self-limiting, serious adverse events including febrile seizures can occur with any vaccine including the acellular pertussis vaccine (Jackson 2002), leading to emergency department visits. The occurrence of post-vaccination fever and discomfort could adversely influence parents' perception of the safety of routine childhood immunizations (Jackson 2011).
See Appendix 1 for a glossary of terms.

Description of the intervention

Paracetamol, also known as acetaminophen, is the most common antipyretic medication used in children for prophylaxis and treatment of post-immunization fever and pain (Cranswick 2000; De Martino 2015; Dhingra 2011). While treating pain and dis-

comfort in children is recommended (Russell 2003), evidence regarding the benefits of treating fever with paracetamol is not conclusive. Suggestions of the benefits for fever and behavioral changes in infants who receive whole-cell diphtheria, pertussis, and tetanus (DPT) vaccine (Ipp 1987; Lewis 1988), diphtheria, tetanus, and acellular pertussis (DTaP) vaccine, and other currently used vaccines (Jackson 2011) need to be considered against the concern that paracetamol use following immunization could lead to reduced immune responses (Prymula 2009). Nevertheless, the use of paracetamol to reduce anxiety related to fever is common (Allotey 2004). Children who have had febrile seizures are given antipyretics following immunization to prevent further seizures, although paracetamol is not effective in preventing febrile seizures (Rosenbloom 2013; Schnaiderman 1993).

Oral paracetamol absorbed via the gastrointestinal tract has a high bio-availability of around 80%. Peak blood levels and temperature reduction is similar in children and adults, occurring after about two hours following the oral dose (Brown 1992; Kelley 1992; Moriarty 2016). A commonly used dose in children is 10 mg/kg to 15 mg/kg every four to six hours orally, with a maximum daily (24 hours) dose of 75 mg/kg (Lane 2015; Van den Anker 2013). Parenteral administration is rarely needed.

Paracetamol in therapeutic doses is generally well-tolerated and has few side effects. Adverse effects are rare and hepatotoxicity is related to overdose (Cranswick 2000; Kelley 1992). Overdosing is particularly concerning when used along with other analgesics and opioids (Graham 2013).

How the intervention might work

Fever is considered to be a response of the body to internal and external stimuli to facilitate effective immunologic defence mechanisms. Neurological and immune responses play a role with endogenous cytokines such as interleukin (IL)-1 beta, IL-6, and tumor necrosis factor-alfa from white blood cells mediating an increase in prostalandin-E2 (PGE2) levels and the anterior hypothalamic thermoregulatory set-point being raised. The fever that results seems to facilitate activation of protective immune mechanisms (Kluger 1995; Kwiatkowski 1995).

The exact pathophysiological processes influenced by paracetamol in controlling fever have not been ascertained. It is postulated that warm-sensitive neurons that initiate heat loss through physiological responses are inhibited by prostaglandins produced during fever (Fields 2013). Paracetamol seems to reduce fever through unblocking these heat-loss neurons by impairing the formation of prostaglandins and fever-causing cytokines in the central nervous system (Feldberg 1973; Mackowiak 1998; Morrison 2011).

Although a weaker analgesic than non-steroidal analgesic medications (Graham 2013), paracetamol is generally preferred for children because it is better tolerated. Analgesic effects of paracetamol are mediated by inhibition of cyclooxygenase-1 and 2 enzymes. This is believed to be achieved through descending serotonergic pathways and by impairing prostaglandin synthesis (Graham 2013; Marzuillo 2014).

Why it is important to do this review

Fever and local reactions, although usually self-limiting over a few days, may cause considerable concern among parents and healthcare professionals (Crocetti 2001; De Bont 2015). Due to the concern of fever and local reaction, paracetamol continues to be prescribed widely despite contrary views on its benefits. Conclusive evidence is also lacking on the beneficial effects of paracetamol in preventing serious complications such as febrile seizures (Rosenbloom 2013). Following a report on the possibility of a reduced immune response to vaccines in children who are given paracetamol for fever prophylaxis (Prymula 2009), routine prophylaxis is no longer recommended in some countries such as Canada and New Zealand (Government of Canada 2016; NZ Ministry of Health 2015). A non-Cochrane systematic review affirmed that there is a reduction in antibody responses to some vaccine antigens with prophylactic use of antipyretics, although this review suggested that such a reduction in immune responses might not be clinically significant (Das 2014). In 2015, with the introduction of a meningococcal vaccine in the UK and Ireland immunization schedules, guidance was issued recommending prophylactic administration of paracetamol to infants around the time of immunization and post-immunization (NHS 2015; Public Health Agency 2015; Public Health Agency (HSE) 2016). Given such continuing uncertainties, this systematic review could help inform clinical and policy decisions on paracetamol given as a prophylactic to prevent fever following vaccination in children.

OBJECTIVES

To evaluate the efficacy and safety of prophylactic paracetamol to prevent fever in children receiving vaccination as part of a childhood immunization schedule.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). We will include studies reported either as full text or as abstract only. We will also include unpublished data.

Types of participants

Healthy children (aged up to 18 years) who received any vaccine as part of an immunization schedule and who did not need paracetamol for any other reason will be included.

Types of interventions

We will include trials that evaluate paracetamol given as a prophylaxis at the time of immunization or after vaccination but prior to onset of fever (NHS 2015).
Dose: single or multiple doses, 10 mg/kg to 15 mg/kg.
Route of administration: oral preparation or rectal suppository.
Comparision: We will consider any of the following for comparison with the intervention:

- No antipyretic prophylaxis or placebo;
- Single dose over 15 mg/kg;
- Multiple doses over 15 mg/kg;
- Any other antipyretic medication;
- Non-pharmacological interventions for fever prophylaxis such as tepid sponging.

Types of outcome measures

Primary outcomes

1. Fever within 24 hours of vaccination (as defined by trialists).
2. Immunogenicity measured by quantitative immunoglobulin assays one month post-vaccination and beyond. Adequacy of immune response will be determined based on standards accepted by the World Health Organization (WHO) (Plotkin 2010; WHO 2013).

Secondary outcomes

1. Fever after 24 hours and up to 72 hours.
2. Serious adverse events (e.g. death, hospitalization, disability etc, as defined by FDA 2016).
3. Visit to accident and emergency department or other outpatient visit to a physician for any adverse event related to immunization.
4. Any adverse event (e.g. nausea, vomiting, behavioral abnormalities).
5. Febrile seizures.
6. Local reaction (site tenderness, redness and swelling, intensity of tenderness).
7. Abnormal cry (prolonged/persistent cry as described by the trialists).
8. Time lost from work (parent/guardian) or school/activities (child).

Reporting of the outcomes listed here will not be an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will conduct a literature search to identify all published and unpublished RCTs. We will not place any restriction on the language or time of publication when searching the electronic databases. We will translate the non-English language papers and fully assess them for potential inclusion in the review as necessary.
We will search the following electronic databases for identifying potential studies:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (1946 to present) (Appendix 2);
- Embase (1974 to present); and
- CINAHL (1937 to present).

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will contact authors of identified trials and ask them to identify other published and unpublished studies. We will also contact manufacturers and experts in the field.

Grey literature databases

We will search the following grey literature databases for theses, dissertations and conference proceedings:

- ProQuest Dissertations & Theses Global;
- Conference Proceedings Citation Index - Science; and
- OCLC PapersFirst.

Clinical trials registers/trial result registers

We will conduct searches of clinical trial registers/trial result registers:

- Clinical Trials.gov; and
- International Clinical Trials Registry Platform Search Portal (WHO).

Data collection and analysis

Selection of studies

Two review authors (RK and AV) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full text study reports/publication and two review authors (RK and AV) will independently screen the full text and identify studies

for inclusion, as well as identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third author (RZK). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and characteristics of excluded studies table.

Data extraction and management

We will use a standard data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Two review authors independently (RK and AV) will extract study characteristics from included studies. We will extract the following study characteristics:

1. Methods: study design, total duration study and run in, number of study centres and location, study setting, withdrawals, date of study.
2. Participants: N, mean age, age range, sex, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria, combined versus single vaccine, age at administration of dose(s), vaccine dose number.
3. Interventions: intervention, comparison, concomitant medications, excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

Two review authors (RK and AV) will independently extract outcome data from included studies. We will note in the characteristics of included studies table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third author (RZK). One review author (RK) will copy data from the collection form into the Review Manager file (Review Manager 2014). We will double check that the data are entered correctly by comparing the study reports with how the data are presented in the systematic review. A second review author will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Review authors (RK and AV) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement will be resolved by discussion or by involving a third author (RZK). We will assess the risk of bias according to the following domains:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessment;
5. Incomplete outcome data;
6. Selective outcome reporting; and
7. Other bias.

We will grade each potential source of bias as high, low, or unclear and provide a quote form the study report together with a justification for our judgement in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary. Where information on risk of bias relates to unpublished data or correspondence with a study author, we will note this in the risk of bias table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse and report dichotomous data as risk ratio and continuous data as mean difference or standardised mean difference (SMD) along with 95% confidence interval (CI). SMD will be used when the same outcomes are measured using different scales. We will ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction of effect to the reader, and report where the directions were reversed if this is necessary.

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense.

A common way authors indicate skewed data is by reporting medians and interquartile ranges. When we encounter this, we will note that the data were skewed and discuss such data descriptively.

Unit of analysis issues

The unit of analysis will be the individual, with a single measurement of each outcome for each participant being collected and analysed. Where multiple study arms are reported in a single study, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) must be entered into the same meta-analysis, we will halve the control group to avoid double counting.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome

data where possible (e.g. when a study is identified as an abstract only).

Assessment of heterogeneity

We will use the I^2 statistic (Higgins 2003) to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity (I^2 > 60%) we will explore causes in pre-specified subgroup analyses.

Assessment of reporting biases

We will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored by a sensitivity analysis**.**

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible publication biases.

Data synthesis

If appropriate we will perform a meta-analysis using the Mantel-Haenszel random-effects method for dichotomous data using Review Manager software (RevMan 2014). We will use the inverse-variance random-effects method for continuous data.

'Summary of findings' table

We will create a summary of findings table for the main comparisons:

1. Paracetamol versus no antipyretic prophylaxis or placebo;
2. Paracetamol standard dose versus higher dose of paracetamol (single or multiple);
3. Paracetamol versus any other antipyretic medication;

using the following primary and secondary outcomes

1. Fever within 24 hours of vaccination (as defined by trialist);
2. Immunogenicity measured by quantitative immunoglobulin assays one month post-vaccination and beyond. Adequacy of immune response will be determined based on standards accepted by the World Health Organization (Plotkin 2010; WHO 2013);
3. Fever after 24 hours and up to 72 hours;
4. Serious adverse events (e.g. death, hospitalization, disability etc, as defined by FDA 2016);
5. Visit to accident and emergency department or other outpatient visit to a physician for any adverse event related to immunization;
6. Any adverse event (e.g. nausea, vomiting, behavioral abnormalities); and
7. Febrile seizures.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the pre-specified outcomes (GRADEpro GDT). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook* (Higgins 2011) and using GRADEpro software. We will justify all decisions to down- or up-grade the quality of studies using footnotes and make comments to aid a reader's understanding of the review where necessary. If meta-analysis is not possible, we will present the results in a narrative format. We will consider whether there is any additional outcome information that was not able to be incorporated into meta-analyses and note this in the comments and state if it supports or contradicts the information from the meta-analyses.

Subgroup analysis and investigation of heterogeneity

We plan to carry out subgroup analyses based on the following characteristics:

1. Vaccine dose number. Pertussis containing vaccine combinations, whole and acellular, produce increasing fever with increasing dose number.
2. Whole-cell or acellular pertussis containing vaccines. Acellular and whole cell pertussis vaccines are available either singly or are combined with diphtheria, tetanus, hepatitis B, Haemophilus influenza B, and Inactivated polio vaccines in various combinations. Of these, single acellular pertussis vaccine and acellular pertussis containing vaccines are known to be less pyrogenic than their whole cell counterparts. Hence, we intend to distinguish whole cell pertussis containing vaccines from acellular pertussis containing vaccines in the analysis.
3. Combination vaccines or simultaneous multiple vaccination. Mumps-measles-rubella-varicella (MMRV) combination vaccine has a greater risk of febrile seizures than when mumps-measles-rubella (MMR) and varicella are given simultaneously and separately.
4. Children aged up to six months, or six months to five years or more. Febrile seizures are common between six months and five years of age. Furthermore, immune responses have been reported to be more robust with advancing age.
5. Paracetamol given every four to six hours or less frequent dosing.

The following outcomes will be used in subgroup analysis:

1. Fever within 24 hours of vaccination.
2. Immunogenicity measured by quantitative Immunoglobulin assays within 30 days.

We will use the interaction test to assess the subgroup difference.

Sensitivity analysis

We will perform sensitivity analysis defined a priori to assess the robustness of our conclusions. This will involve excluding the studies at high risk of bias. We will classify studies as having a high

risk of bias based on random sequence generation and allocation concealment.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will give the reader a clear sense of where the focus of any future research in the area should be and what the remaining uncertainties are.

ACKNOWLEDGEMENTS

We acknowledge the help and support of the Cochrane Upper Gastrointestinal Diseases Review Group, Musculoskeletal Group, and Child Health Field. The authors would also like to thank the following editors and peer referees who provided comments to improve the protocol: Joan Robinson (Editor), Ben Vandermeer, Michael Steiner, Noni Macdonald and Helen Castledine and to Ann Jones for copy editing the protocol.

The methods section of this protocol is based on a standard template used by Cochrane Gastrointestinal and Pancreatic Diseases Review Group.

REFERENCES

Additional references

Allotey 2004
Allotey P, Reidpath DD, Elisha D. "Social medication" and the control of children: A qualitative study of over-the-counter medication among Australian children. *Pediatrics* 2004;**114**(3):e378–83. [PUBMED: 15342901]

Brown 1992
Brown RD, Wilson JT, Kearns GL, Eichler VF, Johnson VA, Bertrand KM. Single-dose pharmacokinetics of ibuprofen and acetaminophen in febrile children. *Journal of Clinical Pharmacology* 1992;**32**(3):231–41. [PUBMED: 1564127]

Cranswick 2000
Cranswick N, Coghlan D. Paracetamol efficacy and safety in children: The first 40 years. *American Journal of Therapeutics* 2000;**7**(2):135–41. [PUBMED: 11319581]

Crocetti 2001
Crocetti M, Moghbeli N, Serwint J. Fever phobia revisited: have parental misconceptions about fever changed in 20 years?. *Pediatrics* 2001;**107**(6):1241–6. [PUBMED: 11389237]

Das 2014
Das RR, Panigrahi I, Naik SS. The effect of prophylactic antipyretic administration on post-vaccination adverse reactions and antibody response in children: A systematic review. *PloS One* 2014;**9**(9):e106629. [PUBMED: 25180516]

De Bont 2015
De Bont EG, Loonen N, Hendrix DA, Lepot JM, Dinant GJ, Cals JW. Childhood fever: A qualitative study on parents' expectations and experiences during general practice out-of-hours care consultations. *BMC family practice* 2015; **16**:131. [DOI: 10.1186/s12875-015-0348-0; PUBMED: 26446754]

De Martino 2015
De Martino M, Chiarugi A. Recent advances in pediatric use of oral paracetamol in fever and pain management. *Pain and Therapy* 2015;**4**(2):149–68. [PUBMED: 26518691]

Dhingra 2011
Dhingra B, Mishra D. Immediate versus as-needed acetaminophen for post-immunisation pyrexia. *Annals of Tropical Paediatrics* 2011;**31**(4):339–44. [PUBMED: 22041468]

FDA 2016
USA Food, Drug Administration. What is a serious adverse event?. www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm (accessed March 17, 2017).

Feldberg 1973
Feldberg W, Gupta KP. Pyrogen fever and prostaglandin-like activity in cerebrospinal fluid. *Journal of Physiology* 1973;**228**(1):41–53. [PUBMED: 4568386]

Fields 2013
Fields E, Chard J, Murphy MS, Richardson M. Assessment and initial management of feverish illness in children younger than 5 years: Summary of updated NICE guidance. *British Medical Journal (Clinical Research Ed.)* 2013;**346**: f2866. [PUBMED: 23697671]

Government of Canada 2016
Government of Canada. Canadian Immunization Guide: Part 1 - Key Immunization Information. Vaccine Administration Practices. healthycanadians.gc.ca/healthy-living-vie-saine/immunization-immunisation/canadian-immunization-guide-canadien-immunisation/index-eng.php September 2014 (accessed September 9, 2016).

GRADEpro GDT [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version (accessed prior to April 22, 2017). Hamilton (ON): GRADE Working Group, McMaster University, 2015.

Graham 2013
Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: Therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* 2013;**21**(3):201–32. [PUBMED: 23719833]

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Ipp 1987
Ipp MM, Gold R, Greenberg S, Goldbach M, Kupfert BB, Lloyd DD, et al. Acetaminophen prophylaxis of adverse reactions following vaccination of infants with diphtheria-pertussis-tetanus toxoids-polio vaccine. *Pediatric Infectious Disease Journal* 1987;**6**(8):721–5. [PUBMED: 3313232]

Jackson 2002
Jackson LA, Carste BA, Malais D, Froeschle J. Retrospective population-based assessment of medically attended injection site reactions, seizures, allergic responses and febrile episodes after acellular pertussis vaccine combined with diphtheria and tetanus toxoids. *Pediatric Infectious Disease Journal* 2002;**21**(8):781–6. [PUBMED: 12192169]

Jackson 2011
Jackson LA, Peterson D, Dunn J, Hambidge SJ, Dunstan M, Starkovich P, et al. A randomized placebo-controlled trial of acetaminophen for prevention of post-vaccination fever in infants. *PloS One* 2011;**6**(6):e20102. [PUBMED: 21698100]

Kelley 1992
Kelley MT, Walson PD, Edge JH, Cox S, Mortensen ME. Pharmacokinetics and pharmacodynamics of ibuprofen isomers and acetaminophen in febrile children. *Clinical Pharmacology and Therapeutics* 1992;**52**(2):181–9. [PUBMED: 1505153]

Kelso 2012
Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. Journal of Allergy and Clinical Immunology 2012; Vol. 130, issue 1:25–43.

Kluger 1995
Kluger MJ, Kozak W, Leon LR, Soszynski D, Conn CA. Cytokines and fever. *Neuroimmunomodulation* 1995;**2**(4): 216–23. [PUBMED: 8963750]

Kwiatkowski 1995
Kwiatkowski D. The biology of malarial fever. *Bailliere's Clinical Infectious Diseases* 1995;**2**(2):371–88.

Lane 2015
Harriet Lane Service (Johns Hopkins Hospital). *The Harriet Lane Handbook: A Manual for Pediatric House Officers*. 20th Edition. Philadelphia: Saunders/Elsevier, 2015. [ISBN 9780323096447]

Lewis 1988
Lewis K, Cherry JD, Sachs MH, Woo DB, Hamilton RC, Tarle JM, et al. The effect of prophylactic acetaminophen administration on reactions to DTP vaccination. *American Journal of Diseases of Children (1960)* 1988;**142**(1):62–5. [PUBMED: 3277388]

Mackowiak 1998
Mackowiak PA, Plaisance KI. Benefits and risks of antipyretic therapy. *Annals of the New York Academy of Sciences* 1998;**856**:214–23. [PUBMED: 9917880]

Marzuillo 2014
Marzuillo P, Calligaris L, Barbi E. Tramadol can selectively manage moderate pain in children following European advice limiting codeine use. *Acta Paediatrica* 2014;**103**(11): 1110–6. [PUBMED: 25041277]

Moriarty 2016
Moriarty C, Carroll W. Paracetamol: pharmacology, prescribing and controversies. *Archives of Disease in Childhood. Education and Practice Edition* 2016;**101** (6):331–4. [DOI: 10.1136/archdischild-2014-307287; PUBMED: 27206455]

Morrison 2011
Morrison SF, Nakamura K. Central neural pathways for thermoregulation. *Frontiers in Bioscience* 2011;**16**:74–104. [PUBMED: 21196160]

NHS 2015
UK National Health Service. Using paracetamol to prevent and treat fever after MenB vaccination. www.gov.uk/government/uploads/system/uploads/attachment_data/file/483408/9413-paracetamol-menB-2page-A4-08-web.pdf (accessed prior to April 22, 2017).

NZ Ministry of Health 2015
Ministry of Health, New Zealand Government. Tips following immunisation. health.govt.nz/your-health/healthy-living/immunisation/tips-following-immunisation December 2015 (accessed September 9, 2016).

Plotkin 2010
Plotkin SA. Correlates of protection induced by vaccination. *Clinical and Vaccine Immunology* 2010;**17**(7):1055–65. [PUBMED: 20463105]

Prymula 2009
Prymula R, Siegrist CA, Chlibek R, Zemlickova H, Vackova M, Smetana J, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: Two open-label, randomised controlled trials. *Lancet* 2009;**374**(9698): 1339–50.

Public Health Agency (HSE) 2016
Public Health Agency, HSE Dublin Ireland. Guidelines for vaccination in general practice. www.hse.ie/eng/health/Immunisation/infomaterials/pubs/guidelinesGP.pdf (accessed March 10, 2017).

Public Health Agency 2015
Public Health Agency, HSC Northern Ireland. Advice on giving infant paracetamol after MenB vaccination. www.publichealth.hscni.net/sites/default/files/Paracetamol_and_MenB_Factsheet_07_15.pdf (accessed September 9, 2016).

Review Manager 2014 [Computer program]
Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration, 2014.

Rosenbloom 2013
Rosenbloom E, Finkelstein Y, Adams-Webber T, Kozer E. Do antipyretics prevent the recurrence of febrile seizures in children? A systematic review of randomized controlled trials and meta-analysis. *European Journal of Paediatric Neurology: EJPN* 2013;**17**(6):585–8. [PUBMED: 23702315]

Russell 2003
Russell FM, Shann F, Curtis N, Mulholland K. Evidence on the use of paracetamol in febrile children. *Bulletin of the World Health Organization* 2003;**81**(5):367–72. [PUBMED: 12856055]

Schnaiderman 1993
Schnaiderman D, Lahat E, Sheefer T, Aladjem M. Antipyretic effectiveness of acetaminophen in febrile seizures: Ongoing prophylaxis versus sporadic usage. *European Journal of Pediatrics* 1993;**152**(9):747–9. [PUBMED: 8223808]

Van den Anker 2013
Van den Anker JN. Optimising the management of fever and pain in children. *International Journal of Clinical Practice* 2013;**Supplement**(178):26–32. [PUBMED: 23163545]

Wallace 2014
Wallace AS, Mantel C, Mayers G, Mansoor O, Gindler JS, Hyde TB. Experiences with provider and parental attitudes and practices regarding the administration of multiple injections during infant vaccination visits: Lessons for vaccine introduction. *Vaccine* 2014;**32**(41):5301–10.

WHO 2013
World Health Organization. Correlates of vaccine-induced protection: Methods and implications. apps.who.int/iris/bitstream/10665/84288/1/WHO_IVB_13.01_eng.pdf 2013 (accessed September 27, 2016).

WHO 2015
World Health Organization. Global Vaccine Safety. WHO vaccine reaction rates information sheets. www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/ 2015 (accessed March 7, 2017).

WHO 2016
World Health Organisation. Summary of WHO Position Papers - Recommendations for Routine Immunization. who.int/immunization/policy/immunization_tables/en/ (accessed September 9, 2016).

Zhang 2014
Zhang L, Prietsch SOM, Axelsson I, Halperin SA. Acellular vaccines for preventing whooping cough in children. *Cochrane Database of Systematic Reviews* 2014, Issue 9. [DOI: 10.1002/14651858.CD001478.pub6]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Glossary of terms

Acellular pertussis vaccine: whooping cough vaccine in which only components of bacterial cells are present and not whole cells
Antipyretics: medications given to prevent or treat fever
Booster: additional doses of a vaccine given to 'boost' the immune system
Immunogenicity: ability of the vaccine to generate protective responses against infections
MMR: mumps, measles, rubella
MMRV: mumps, measles, rubella, varicella
Paracetamol: name of the medicine commonly used to reduce fever (also known as acetaminophen)
Parenteral administration: medications given by any route other than by mouth, such as injections into the skin, under the skin, or into the muscles or veins
Whole-cell pertussis vaccine: whooping cough vaccine in which whole cells of bacteria are present

Appendix 2. MEDLINE search strategy

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
1. Immunization/ (47489)
2. Diphtheria Toxoid/ (3014)
3. exp Vaccination/ (73138)
4. exp Vaccines/ (202973)
5. (booster* or immuni* or innoculat* or preimmuni* or postimmuni*).tw,kf. (275019)
6. (bOPV* or IPV* or OPV* or HAV or Hib or MMR* or MCV* or prevaccine* or postvaccine* or RCV* or vaccine*).tw,kf. (214973)
7. (diphtheria* or dtap* or DTP*).tw,kf. (29287)
8. (prevaccinat* or postvaccinat* or vaccinat*).tw,kf. (128790)
9. or/1-8 [Combined MeSH & text words for vaccination] (548199)
10. exp Adolescent/ (1788868)
11. exp Child/ (1718426)
12. exp Infant/ (1037223)
13. exp Minors/ (2369)
14. exp Pediatrics/ (51718)
15. (adolescen* or boy* or girl* or minors or teen*).tw,jw,kf. (439158)
16. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).tw,jw,kf. (796780)
17. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).tw,jw,kf. (1294023)
18. p?ediatric*.tw,jw,kf. (621346)
19. or/10-18 [Combined MeSH & text words for adolescents & children] (3879644)
20. and/9,19 [Combined search strings for population concept] (120404)
21. Acetaminophen/ (15739)
22. Antipyretics/ (2447)
23. Fever/dt, pc [Drug Therapy, Prevention & Control] (4723)
24. Seizures, Febrile/dt, pc [Drug Therapy, Prevention & Control] (566)
25. (362O9ITL9D or acetaminophen*).tw,kf,rn. (20438)
26. (anti-pyretic* or antipyretic*).tw,kf. (6330)
27. (febrile and (control* or drug* or interven* or medic* or prevent* or prophyla* or treat* or therap*)).tw,kf. (19261)
28. (fever* and (control* or drug* or interven* or medic* or prevent* or prophyla* or treat* or therap*)).tw,kf. (82160)
29. paracetamol*.tw,kf. (9654)
30. tylenol*.tw,kf. (177)
31. or/21-30 [Intervention concept of prophylactic paracetamol] (124608)
32. and/20,31 [Combined population and intervention concepts] (3123)
33. randomized controlled trial.pt. (434822)
34. controlled clinical trial.pt. (91892)
35. randomized.ab. (375818)
36. placebo.ab. (180951)
37. drug therapy.fs. (1923428)
38. randomly.ab. (266794)
39. trial.ab. (391050)
40. groups.ab. (1657086)
41. or/33-40 (3940072)
42. exp animals/ not humans.sh. (4337105)
43. 41 not 42 (3399561)
44. and/32,43 [Filter applied: Cochrane Highly Sensitive search strategy for identifying randomized trials - http://handbook.cochrane.org/] (1212)
45. remove duplicates from 44 (1169)

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: RK, AV, RZK

Designing the protocol: RK, AV, RZK

Coordinating the protocol: RK, AV, RZK

Designing search strategies: Child Health Field Information Specialist

Writing the protocol: RK; AV and RZK

Providing general advice on the protocol: RZK

Performing previous work that was the foundation of the current study: RZK

DECLARATIONS OF INTEREST

Richard Kirubakaran: none known

Anand Viswanathan: none known

Rajeev Z Kompithra: none known

SOURCES OF SUPPORT

Internal sources

- Christian Medical College, Vellore, India.

Salary and logistic support for RZK and logistic support for RK and AV.

External sources

- UKaid (Department for International Development), UK.

Grant to Cochrane South Asia via the Effective Health Care Research Consortium (EHCRC), Liverpool School of Tropical Medicine (LSTM)